

suggestive of multiple sclerosis. *Cochrane Database Syst Rev* 2017;4:CD012200.

DOI: 10.1056/NEJMc1708486

THE AUTHORS REPLY: Benedetti et al. suggest weaknesses of our trial. Despite debate among statisticians, stratified and regression analyses are commonly used to adjust the estimate of treatment effect for confounding variables that have arisen because of imbalanced prognostic factors between trial groups.¹ A thorough examination of these variables was carried out in our trial, and only the number of enhancing lesions affected the estimate of treatment effect (Table S5 in the Supplementary Appendix of our article, available at NEJM.org). Multifocal symptom onset was not considered because it does not consistently influence prognosis. Although adjustment for the number of enhancing lesions attenuated the treatment effect, the risk of conversion from a clinically isolated syndrome to multiple sclerosis remained significantly lower with minocycline than with placebo over a period of 6 months.

The RECYCLINE trial mentioned by Benedetti and colleagues was underpowered and evaluated minocycline as an add-on therapy to treatment with interferon beta-1a. The lack of an additive effect in that trial is not evidence that minocycline alone is ineffective.²

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Since publication of their article, the authors report no further potential conflict of interest.

1. Austin PC, Manca A, Zwarenstein M, Juurlink DN, Stanbrook MB. A substantial and confusing variation exists in handling of baseline covariates in randomized controlled trials: a review of trials published in leading medical journals. *J Clin Epidemiol* 2010;63:142-53.
2. Sørensen PS, Sellebjerg F, Lycke J, et al. Minocycline added to subcutaneous interferon β -1a in multiple sclerosis: randomized RECYCLINE study. *Eur J Neurol* 2016;23:861-70.

DOI: 10.1056/NEJMc1708486

Adalimumab for Uveitis in Juvenile Idiopathic Arthritis

TO THE EDITOR: Ramanan et al. (April 27 issue)¹ found that adalimumab combined with orally administered methotrexate resulted in a lower rate of treatment failure among children with uveitis and juvenile idiopathic arthritis than did methotrexate alone. There exist differences in the bioavailability of methotrexate when it is administered orally versus when it is administered subcutaneously.² A clinical trial of orally administered methotrexate for rheumatoid arthritis showed that oral doses of more than 15 mg per square meter of body-surface area per week did not significantly increase the plasma concentration of methotrexate, and the bioavailability of oral methotrexate has been observed to decrease by as much as 30% with weekly doses exceeding 15 mg.³ We wonder whether the limited bioavailability of a 20-mg dose of oral methotrexate explains the equivalent efficacy of methotrexate doses of 10 mg per week and 20 mg per week in combination with adalimumab in the trial conducted by Ramanan et al. and whether the au-

thors carried out pharmacokinetic measures of the two drugs during the course of their trial.

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No potential conflict of interest relevant to this letter was reported.

1. Ramanan AV, Dick AD, Jones AP, et al. Adalimumab plus methotrexate for uveitis in juvenile idiopathic arthritis. *N Engl J Med* 2017;376:1637-46.
2. Zeidler H. The issue of bioavailability of oral low dose methotrexate: should we choose only 10 mg of MTX a week in conjunction with anti-TNF therapy? *Ann Rheum Dis* 2014;73(8):e50.
3. Schiff MH, Jaffe JS, Freundlich B. Head-to-head, randomised, crossover study of oral versus subcutaneous methotrexate in patients with rheumatoid arthritis: drug-exposure limitations of oral methotrexate at doses ≥ 15 mg may be overcome with subcutaneous administration. *Ann Rheum Dis* 2014;73:1549-51.

DOI: 10.1056/NEJMc1708646

THE AUTHORS REPLY: We agree with Peng et al. that the bioavailability of methotrexate is greater

when it is administered subcutaneously than when it is taken orally.¹ In the context of pediatric care, the choice of methotrexate depends on the child's wishes and the child's ability to cope with weekly subcutaneous injections. When feasible, most pediatric rheumatologists will attempt to tailor the administration of methotrexate, including a trial of subcutaneous injection, before considering biologic drugs.

In our trial, we did not specify that children had to be receiving methotrexate subcutaneously, in order to avoid restricting our ability to enroll participants and in view of issues of acceptability regarding the subcutaneous route in some children. We did not undertake phar-

macokinetic studies of either methotrexate or adalimumab in this trial.

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Since publication of their article, the authors report no further potential conflict of interest.

1. Jundt JW, Browne BA, Fiocco GP, Steele AD, Mock D. A comparison of low dose methotrexate bioavailability: oral solution, oral tablet, subcutaneous and intramuscular dosing. *J Rheumatol* 1993;20:1845-9.

DOI: 10.1056/NEJMc1708646

Adjuvant Capecitabine for Breast Cancer

TO THE EDITOR: Masuda et al. (June 1 issue)¹ report the results of the Capecitabine for Residual Cancer as Adjuvant Therapy (CREATE-X) trial. They conclude that the use of capecitabine in patients who have human epidermal growth factor receptor 2 (HER2)-negative breast cancer with residual disease after neoadjuvant chemotherapy prolonged disease-free survival and overall survival and was associated with expected toxic effects. This trial provides practice-changing evidence, predominantly for women with triple-negative disease. However, the value of capecitabine in patients with hormone-receptor-positive disease remains uncertain. Hormone-receptor-positive cancers, which occur in approximately 70% of patients with residual disease, are less responsive to chemotherapy than hormone-receptor-negative cancers.^{2,3}

The Suppression of Ovarian Function Trial (SOFT) and the Tamoxifen and Exemestane Trial (TEXT) showed that premenopausal patients with hormone-receptor-positive breast cancer who remained premenopausal after receiving chemotherapy constituted a particularly high-risk subgroup of patients who benefited from endocrine therapy with ovarian suppression plus tamoxifen or an aromatase inhibitor.^{4,5} Premenopausal women who received adjuvant endocrine therapy constituted 41% of the patients in the CREATE-X trial. A subgroup analysis was performed according to the use of endocrine therapy, but the type of therapy was not specified.

Capecitabine may have benefited premenopausal patients with hormone-receptor-positive disease by increasing the rate of chemotherapy-induced menopause. If the use of ovarian suppression was more common in the placebo group than in the capecitabine group, it may have offset the observed benefit of capecitabine. Was the use of endocrine therapy combined with ovarian suppression well distributed among the subgroups?

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No potential conflict of interest relevant to this letter was reported.

1. Masuda N, Lee S-J, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. *N Engl J Med* 2017;376:2147-59.

2. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet* 2014;384:164-72.

3. Ruades Ninfea JI, Burdette-Radoux S, Sands M, et al. Low dose metronomic cyclophosphamide, methotrexate (LDCM) and aspirin for patients with residual disease after neoadjuvant chemotherapy for stage II-III breast cancer. *J Clin Oncol* 2016;34(15) Suppl:e12040. abstract.

4. Francis PA, Regan MM, Fleming GF, et al. Adjuvant ovarian suppression in premenopausal breast cancer. *N Engl J Med* 2015; 372:436-46.